with **Bang** et al. and **Esmon** et al, and further in view of **Stocker** et al. Applicants respectfully traverse these rejections.

Galin et al. provides for an invention concerning a 'Medicament Coated Intraocular Lens'. The **Galin** et al. invention discloses an opthalmic prosthetic device to be surgically implanted. The medicament treatment is to reduce problems subsequent to trauma to the eye (i.e. due to surgical implantation of the lens). **Galin** et al. disclose the medicament treatment in the form of either sulfated polysaccharides or ethacrylic acid, which may act as an anti-coagulant, anti-inflammatory or anti-complement. **Galin** et al. state that the "principal object of the present invention is to provide an improved intraocular lens" (column 1, lines 42-43) (emphasis added).

Applicants submit that the instant specification actually addresses the situation that **Galin** et al. describe; "the possible causes for postoperative fibrinous membrane formation include...reactions to the intraocular implants and their coating material..." (page 2, lines 3-6). This statement inherently demonstrates the utility of the present invention and makes a clear distinction between the methodology disclosed in the present invention and the **Galin** et al. invention.

Iverson et al. teach that intraocular fibrin formation, often due to tissue injury during eye surgery, may be inhibited by infusion with low-molecular-weight heparin. Iverson et al. is a comparison of intraocular fibrinolysis following treatment with native heparin or low-molecular-weight heparin. **Iverson** et al. admit that "although effective, these methods are associated with complications . . ." (see the middle column on page 405), but **Iverson** et al. do not suggest or teach an alternative to heparin for ocular fibrinolysis.

Bang et al. disclose DNA encoding human protein C and an assay for protein C activity. In summarizing the utility of the **Bang** et al.

invention, the specification states "to be used in an assay for protein C in blood plasma" (sentence bridging columns 13-14), to be used for diagnostic purposes in patients with coagulation problems (column 14, lines 4-5), and "useful in the prevention and treatment of a wide variety of acquired disease states involving intravascular coagulation, including deep vein thrombosis, pulmonary embolism, peripheral arterial thrombosis, emboli originating from the heart or peripheral arteries, acute myocardial infarction, thrombotic strokes, and disseminated intravascular coagulation" (column 19, lines 4-11). Furthermore, **Bang** et al. state that "the protein C composition can be administered parenterally, or by other methods that ensure its delivery to the bloodstream in an effective form" (emphasis added) (column 21, lines 52-55).

In contrast, Applicants' methods of administration of protein C for inflammation of the eye are not parenteral. Applicants submit that claim 25 is directed towards the methods of administration for the present invention, and include topical administration, subconjuctival injection, intracameral injection and intravitreal injection. **Bang** et al. also teach that protein C can "enhance the lysis of fibrin in human whole blood and recent experiments suggest that this effect is mediated through the interaction with a newly discovered inhibitor of tissue plasminogen activator" (see sentence bridging columns 1-2). **Bang** et al. do not teach that this inhibitor would be present in the aqueous humor, the vitreous humor, or the optical environment in general. Therefore, **Bang** et al. do not provide a reasonable expectation that protein C would be effective occularly.

Esmon et al. teaches treatment of cancerous tumors using an inhibitor of protein C (to be provided in combination with a cytokine, e.g., TNF). The Examiner states that **Esmon** teaches that TNF causes inflammatory changes at the endothelial cells and also stimulates

microvascular thrombosis and that activated protein C reduces the production of TNF. However, Applicants respectfully point out that **Esmon** et al. do not teach the presence of TNF in the ocular environment, nor that this biochemical cascade of events similarly occurs in the aqueous and/or vitreous humor of the eye. Significantly, **Esmon** et al. utilizes canines to determine the effects of protein C on tumor inhibition. However, **Esmon** et al. admit that the "natural fibrinolytic system in dogs is very potent" (see column 17, line 17), which results in a blood plasma environment unlike that of humans. Therefore, Applicants submit that very little can be gleaned from the results of **Esmon** et al. and **Esmon** et al. do not render obvious claims 22-29.

Stocker et al. teach a method for assaying protein C and discloses an "activator preparation", which converts the inactive zymogen form of protein C into the active form. **Stocker** et al. teach that their "activator preparation...caused no clotting within 10 minutes and, tested on a non-heated human fibrin plate, no fibrinolysis within 15 hours" (see column 6, lines 55-58) (emphasis added). Thus, **Stocker** et al. actually teach away from the utility of protein C in fibrinolysis as disclosed in the instant specification.

Stocker et al. further teach that "the action of protein C is potentiated by protein S, phospholipid and calcium and is inhibited by a specific inhibitor contained in plasma" (column 1, lines 16-18). As in **Bang** et al., **Stocker** et al. do not teach the presence or absence of this inhibitor in the aqueous/vitreous humor of the eye. Therefore, it would not have been obvious to one of ordinary skill from the **Stocker** et al. disclosure that protein C would be effective in fibrinolysis in the ocular environment. Furthermore, Applicants submit that **Stocker** et al. does not teach the

biochemical fidelity of protein S, nor its interaction with protein C, when used in an ocular environment.

On page 3 of the October 14, 1997 Office Action, the Examiner writes that "Applicants' arguments regarding the formation of the thrombin-thrombomodulin complex and the subsequent fibrin formation cascade of reactions are not found to be persuasive since first of all instant claims are drawn to a method of treatment of inflammation and not the pathway leading to the antithrombotic effect". Applicants would like to clarify some of the statements made in the June 13, 1997 Response to the Office Action. The Examiner is correct that the instant claims are drawn to a method of treatment of inflammation and not the actual pathway leading to the antithrombotic effect described by Applicants. However, because the role of thrombomodulin in ocular tissue had not been demonstrated prior to this application, it was not obvious that protein C would be an effective treatment for inflammation in the eye.

The Examiner goes on to write that "the cascade of chemical reactions and the subsequent fibrin formation is a vascular phenomenon and not dependent on the tissue". Although the cascade of chemical reactions and the subsequent fibrin formation is generally a vascular phenomenon, Applicants note that the instant specification states "the exact pathogenesis of the . . . fibrin responses remains unknown" (see page 2, lines 7-8). Applicants submit that there are many biological reasons a cascade reaction may be disrupted in a tissue specific manner (i.e. the presence of tissue specific inhibitor(s), a tissue-specific absence of a required co-factor, etc.). These features of the ocular environment, and hence their effect on protein C, were unknown prior to this invention.

The cited, either alone or in combination, do not render obvious the claimed invention. Furthermore, one of ordinary skill in the art would

not have combined these particular references to produce the present invention. One of ordinary skill in the art would not have had a reasonable expectation of success in pharmacological applications of protein C in the aqueous humor or vitreous humor of the eye. None of the cited references teach or suggest the ophthalmologic uses for protein C of the present invention. Several of the citations relate to vascular uses of protein C Although optical tissue is obviously vascularized, Applicants contend that the optical environment, particularly that of the aqueous and vitreous humor, is unlike the whole blood or plasma environment described in the prior art cited by the Examiner. Therefore, the prior art could not make obvious the ophthalmologic applications of protein C.

This is intended to be a complete response to the Office Action mailed October 14, 1997. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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